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NICOTINE AND CIGARETTE SMOKING: AN ALTERNATIVE HYPOTHESIS

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ABSTRACT

A new hypothesis is presented to explain some aspects of human smoking behaviour. While acknowledging the importance of the nicotine self-titration phenomenon, changes in puffing intensity during the smoking of a single cigarette are related not to the control of nicotine uptake but to the modification of cigarette smoke composition prior to inhalation. It is suggested that nicotine, in addition to its central effects, has the local action of reducing the acute airway response to irritant components of cigarette smoke. The new hypothesis explains some of the 'anomalous' results of smoking behaviour research, and has implications both for cigarette design and for the recommendations made to smokers by statutory health agencies.

INTRODUCTION

There now exists a substantial body of evidence that supports the view that smoking provides a method of nicotine self-administration (1). The dose of nicotine (and of other ingredients) in the smoke obtained from a cigarette will depend not only on the 'strength' of the cigarette but also on the intensity with which it is smoked. The term intensity encompasses variables such as puffing (puff-volume and frequency of puffing), inhaling (depth and duration of inhalation) and butt length (amount of the cigarette left unsmoked): these are all amenable to voluntary control by the smoker, and may influence the amount of nicotine absorbed from a single cigarette. Furthermore, in analogy to models of drug dependence it has been argued that smokers control their smoke intake to achieve and maintain a desired plasma concentration of nicotine. This regulatory phenomenon, presumably mediated by the action of nicotine on the central nervous system, is termed 'self-titration' (2). Nicotine is metabolised in the human body with a half-life in plasma of about 20 minutes (3), and the average smoker consumes at least one cigarette per hour, thus it seems probable that the frequency of cigarette consumption, conventionally measured in cigarettes per day, is an important additional variable that in combination with cigarette nicotine yield, puffing, inhaling and other characteristics, determines both plasma nicotine levels and the overall rate of uptake of nicotine.

The relationships between the above-mentioned variables can be combined in a simple 'systems' model of nicotine homeostasis (Figure 1). In

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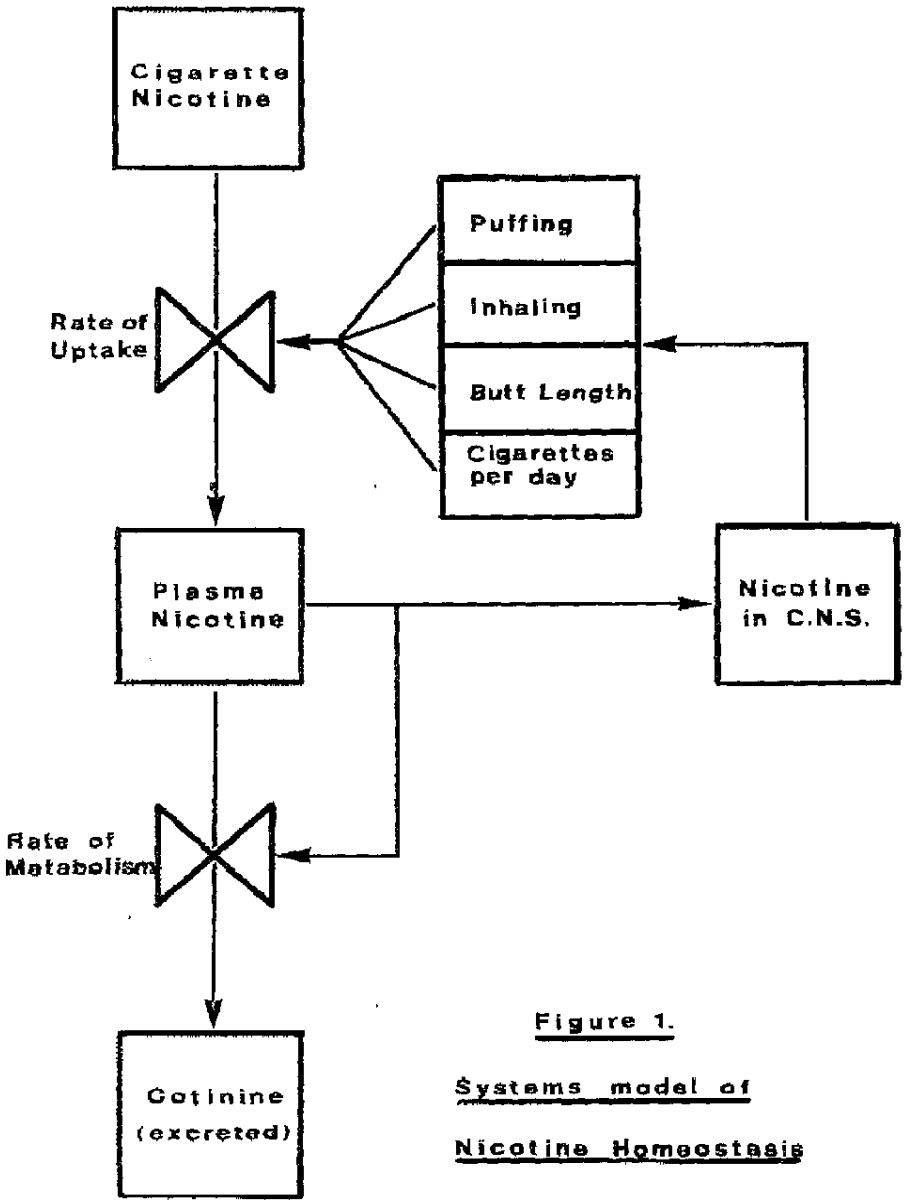

Figure 1.

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this model nicotine uptake is determined by plasma nicotine concentration via a negative feedback loop mediated by the central nervous system and acting on smoking behaviour. Nicotine metabolism is assumed to be concentration-dependent and will thus equilibrate with the rate of uptake of nicotine. In principle, the perturbation of any component of this model should produce a compensatory change in the rate-controlling parameters (puffing, inhaling, overall cigarette consumption) in a direction that minimises any change in plasma nicotine levels. This theoretical consideration has led to a diverse range of experimental procedures being employed in testing the nicotine self-titration hypothesis. Changes in smoking behaviour have been monitored following manipulation of cigarette nicotine yield (4-14), plasma nicotine concentration (15,16), urinary pH (which affects nicotine/cotinine equilibration (17)) and following the administration of nicotine antagonists (18). The results of these experiments by no means provide more than equivocal support for the nicotine self-titration hypothesis (19): intravenous administration of nicotine may decrease overall cigarette consumption (15) but has no observable effect on the intensity with which individual cigarettes are smoked (16). Similarly, out of the 17 'brand-switching' experiments (4-14) known to the authors, only 11 yielded the expected compensatory response in puff volume following changes in cigarette nicotine yield. Furthermore, a study designed to identify the separate effects of cigarette tar and nicotine yield on puffing intensity showed that when tar yield was statistically controlled for, smokers of cigarettes with higher yields of nicotine took <u>larger</u> puffs of smoke from their cigarettes than did smokers of cigarettes with lower yields of nicotine (20).

We believe that the experimental evidence is consistent with smokers 'compensating' for changes in nicotine uptake by regulating the numbers of cigarettes smoked per day (21), although it should be noted that estimates of individual daily cigarette consumption rely on subjects' self-reports (subjects are rarely monitored in the laboratory for more than a few hours at a time) and therefore constitute less reliable data than is provided by measurements of smoking intensity taken under controlled laboratory conditions. It is our further belief that changes in puffing intensity do <u>not</u> play a primary role in the titration of nicotine uptake. In our view, differences in puffing intensity, which are observed during the smoking of a single cigarette (10) as well as between cigarettes of different tar and nicotine yields, reflect an attempt by the smoker to exercise control over the relative proportions of tobacco smoke ingredients prior to inhalation. We propose that nicotine, in addition to its central effects, has the local action of suppressing an acute airway response to irritant components of tobacco smoke, and we infer that smoking patterns resulting in an increase in the nicotine concentration of individual smoke particles will be reinforced by the accompanying reduction in irritant response. The nicotine concentration in the particulates is paradoxically a function of both tar and nicotine yields, since the tar yield is calculated as the dry weight of particulates after nicotine extraction: nicotine concentration can be approximated by dividing nicotine yield by the sum of tar and nicotine yields. Our new hypothesis, and some of the important testable deductions that can be

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drawn from it, are presented in more detail below.

THE HYPOTHESIS

The irritant properties of cigarette smoke, and the paradox of inhalation

Cigarette smoke is an 'irritant' to bronchial epithelium, and it remains a paradox that smokers are able to inhale smoke. On inhalation, cigarette smoke can initiate bronchoconstriction via a vagal reflex (22,23) and it appears that the degree of bronchoconstriction increases with the amount of 'tar' or particulate matter in the smoke (22,24,25). Yet in several large scale studies in which smokers were allowed to smoke in an unconstrained fashion little acute bronchoconstriction was recognised (26,27). The pattern of 'normal' smoking suggests that smokers are able to modify the constituents of smoke to lessen its irritant qualities prior to inhalation: the puff of smoke is held for a short period in the mouth, allowing some water-soluble ingredients to be absorbed (28), and the puff is further diluted with room air before it is inhaled (29). We propose that in addition to these recognised means by which acute bronchoconstriction might be avoided, the smoker can control the nicotine concentration of the smoke by modifying the intensity with which he puffs at the cigarette. We believe that the purpose of this proposed mechanism is to counteract the irritant qualities of the smoke (which we equate with the particulates) by increasing the fraction of those particulates which are present as nicotine. An animal study has shown that nicotine administered as an aerosol depresses bronchial reactivity to metacholine (a chemical analogue of acetylcholine) (30), implying that nicotine might be able to suppress the vagally-mediated bronchial irritant reflexes. Whether the same is true in man remains uncertain, although there is evidence that chronic exposure to cigarete smoke also suppresses 'irritant' airway responses, as some young smokers have reduced bronchial responses to inhaled histamine (31).

We suggest therefore that smokers may attempt to balance the amount of tar and the amount of nicotine in the smoke which they draw from a cigarette in order to facilitate the subsequent inhalation. It is the nicotine concentration in the particles of smoke, rather than the overall nicotine yield of the cigarette, that in our view is the principal determinant of the amount of smoke puffed (and by implication inhaled) from a cigarette. Furthermore, our hypothesis would predict that smokers, while smoking a single cigarette, will alter their pattern of puffing in response to the increase in tar to nicotine ratio (and hence decline in nicotine concentration) that is known to occur as a cigarette is progressively consumed (32).

Changes in smoke, and changes in smoking, within the cigarette

The published yields of tar, nicotine and other ingredients of cigarette smoke are determined using smoking machines which smoke cigarettes in a standard, reproducible fashion. Unlike human smokers, these machines maintain a constant puff volume, puff duration and puff interval throughout the 5-10 minute period between lighting the

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cigarette and extinguishing it at a preset butt length. Under these 'standard' smoking conditions, proportionately more tar and less nicotine is delivered as the cigarette burns, leading to an increase in the ratio of tar to nicotine in the smoke (32), reflecting a reduction in nicotine concentration in the particulates. Human smokers by contrast reduce puff volume and increase the intervals between puffs as the cigarette is progressively smoked (10,33-35). This direction of change in puff volume and frequency of puffing, amounting to a reduction in puffing intensity, markedly reduces the ratio of tar to nicotine in the smoke (36,37). We propose that human smokers, by progressively reducing the intensity of puffing as the cigarette burns, are able to stabilise the concentration of nicotine in the particulates at a desired level - certainly, machine duplication of the actual puffing patterns used by humans shows that human smokers derive proportionately more nicotine from a cigarette than does the machine operating under 'standard' conditions (6).

If this response to within-cigarette changes in smoke composition is an important aspect of the human physiological adaptation to smoking, we would expect to observe the same pattern of differences in puffing intensity among smokers of cigarettes yielding different proportions of tar and nicotine, and we would also expect smokers to change their intensity of puffing when they switch from their usual cigarette to a product with a different ratio of tar to nicotine. The nicotine self-titration hypothesis makes neither of these predictions, since it links puffing intensity solely to the nicotine yield of the cigarette.

Differences in smoke, and differences in smoking between cigarettes

In a study designed to identify factors influencing the manner in which cigarettes are smoked, Sutton and coworkers (20) recorded the puffing patterns of smokers of a wide range of cigarettes. A multiple regression analysis was used to compare the separate effects of cigarette tar and nicotine yield on the total volume of smoke puffed from the cigarette (total volume puffed is a summary measure of puffing intensity, combining puff volume and interval between puffs). When the tar yield was statistically controlled for, smokers of cigarettes with higher yields of nicotine puffed larger volumes of smoke from their cigarettes. Conversely when nicotine yield was controlled for, smokers of higher tar cigarettes puffed smaller volumes of smoke. The authors noted that these results were not consistent with the nicotine self-titration hypothesis, and interpreted their findings as evidence for smokers 'compensating' for tar yield differences over and above any compensation for differences in nicotine yield. Our interpretation of this important study is very different. Variation in tar yield and in nicotine yield have separate and opposite effects on the nicotine concentration in the smoke, and would be expected, by our hypothesis, to have separate and opposite effects on the volume of smoke puffed from a cigarette. Our hypothesis predicts that increasing nicotine while holding tar constant will reduce the 'irritant' properties of cigarette smoke, allowing more intensive puffing - the nicotine self-titration hypothesis would predict less intensive puffing as nicotine levels increase.

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Table I: Data from brand-switching studies in which details of cigarette yields and measurements of puffing were given.

Year	Authors	No. of Subjects	Time to Adapt (days)	Cigarette Strength	Tar Yield (mg.)	Nicotine Yield (mg.)	Particulates (T+N) (mg.)	Nicotine % (N/T+N) (percent)	Puff Volume (ml.)	Puff Frequency (min^{-1})	Total Vol. Puffed (ml.)
1971	Frith	9	1	medium	17.1	1.17	18.5	7.41	*14.7	3.18	*269
				low	14.6 (↓)	1.02 (↓)	15.6	6.54 (↓)	*12.1 (↓)	3.24 (↑)	*218 (↓)
				high	30.8 (↑)	2.11 (↑)	32.9	6.41 (↓)	*12.7 (↓)	2.58 (↓)	*228 (↓)
1978	Adams	20	28	medium	25	1.4	26.4	5.30	32.8	1.71	364
				low	12 (↓)	0.8 (↓)	12.8	6.25 (↑)	39.1 (↑)	1.86 (↑)	469 (↑)
1978	Creighton & Lewis	16	28	medium	23.3	1.4	24.7	5.67	45.1	1.55	543
				low	16.1 (↓)	1.0 (↓)	17.1	5.85 (↑)	53.4 (↑)	1.61 (↑)	625 (↑)
				high	35.7 (↑)	1.8 (↑)	37.5	4.80 (↓)	39.6 (↓)	1.64 (↑)	433 (↓)
1978	Dunn & Freiesleben	4	3	control	19.9	1.01	20.9	4.84	43.6	1.93	417
				med T/high N	21.4 (↑)	1.32 (↑)	22.7	5.81 (↑)	45.1 (↑)	1.98 (↑)	435 (↑)
1978	Guillerm & Radziszewski	8	7	control	30.9	1.66	32.6	5.10	38.5	1.85	452
				experimental	15.9 (↓)	1.31 (↓)	17.2	7.61 (↑)	34.8 (↓)	1.85 (=)	485 (↑)
1978	Rawbone et al.	9	28	usual	17.1	1.22	18.3	6.66	42.4	1.55	408
				low	9.0 (↓)	0.83 (↓)	9.8	8.44 (↑)	50.5 (↑)	1.38 (↓)	512 (↑)

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1981	Stepney	19	14	usual	19	1.55	20.5	7.55	37.6	1.93	485
				low	11 (↓)	0.7 (↓)	11.7	5.98 (↓)	45.4 (↑)	1.98 (↑)	548 (↑)
				low T/ mac N	10 (↓)	1.1 (↓)	11.1	9.91 (↑)	45.5 (↑)	1.87 (↓)	560 (↑)
1981	Herning et al.	24	0	medium	24.5	1.17	25.7	4.55	35.9	2.23	564
				low	31.8 (↑)	0.42 (↓)	32.2	1.30 (↓)	47.8 (↑)	2.02 (↓)	736 (↑)
				high	29.6 (↑)	2.5 (↑)	32.1	7.79 (↑)	36.9 (↑)	2.00 (↓)	620 (↑)
1982	Gust & Pickens	6	0	medium	24.5	1.25	25.7	4.86	44.4	1.16	382
				low	24.7 (↑)	0.32 (↓)	25.0	1.28 (↓)	50.8 (↑)	1.09 (↓)	379 (↑)
				high	29.6 (↑)	2.50 (↑)	32.1	7.80 (↑)	36.8 (↑)	0.96 (↓)	247 (↓)
1982	Russell et al.	12	1-2	usual	17.4	1.33	18.7	7.10	39.8	2.34	547
				low	10.9 (↓)	0.7 (↓)	11.6	6.04 (↓)	38.5 (↓)	2.12 (↓)	549 (↑)
				medium	19.0 (↑)	1.3 (↓)	20.3	6.40 (↓)	38.8 (↓)	2.11 (↓)	569 (↑)
1982	Tobin & Sackner	10	0	high	26	1.8	27.8	6.48	39	No data	324
				low	4 (↓)	0.4 (↓)	4.4	9.10 (↑)	52 (↑)	No data	437 (↑)

Arrows indicate direction of change relative to the "usual", "control", or "medium" brand. In Tobin & Sackner's study the "high" cigarette is considered more representative of their subjects' usual brands. In Frith's study smoke volumes (asterisked) were given in arbitrary units.

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Clearly Sutton and coworkers' results are evidence in favour of our hypothesis: nevertheless, it could be argued that a single, cross-sectional study might be biased in its selection of subjects, perhaps because smokers of low-tar cigarettes differ constitutionally from other smokers. We have therefore examined the data from all published 'brand-switching' studies in which puffing patterns were monitored before and after smokers 'switched' between cigarettes of known, different yields. As noted above, smokers appear to increase their rate of cigarette consumption, measured as cigarettes smoked per day, when they switch to cigarettes with lower nicotine yields (21), and we recognise this phenomenon as a self-titration mechanism. We question, however, whether the increased intensity of puffing which also may be observed on switching to low-yield cigarettes is similarly attributable to nicotine homeostasis: compared to medium-strength products, cigarettes with a low machine-smoked yield contain tobacco with a higher nicotine concentration (38) and despite their lower yield of nicotine the smoke particulates paradoxically may have a higher concentration of nicotine than particulates generated by medium strength products.

Eleven 'switching' studies are known to the authors in which changes in puff volume were monitored - together these document a total of 17 changes between brands, and are listed in Table 1 (4-14). From each study we extracted data on the tar and nicotine yields of the cigarettes together with the mean puff volume, puff frequency and total volume puffed both before and after brand-switching. For one study (9), the cigarette yields were not published, but the values were obtained by personal communication with the author. The studies varied in the number of subjects monitored and in the period over which the subjects accustomed themselves to the different cigarettes: furthermore, two studies (11,12) used research cigarettes with yields falling outside the range of commercially available brands. In view of these differences in methodology we have restricted our analysis to a simple chi-squared test of association between the direction of change in nicotine and the direction of change in puffing intensity, in an attempt to determine whether measures of puffing intensity are better predicted by the nicotine yield of the cigarette or by the nicotine concentration in the smoke. The values of chi-squared are given in Table 2: although none of the values achieves statistical significance at the conventional $P < 0.05$ level (perhaps as a result of the small sample size) there appears to be a relationship between the directions of change in cigarette smoke composition and volume-related measures of puffing intensity, and that for puff volume at least, the association between puff volume and nicotine concentration in the smoke is stronger than the association between puff volume and nicotine yield, marginally favouring our hypothesis. Clearly, in brand-switching studies there are confounding factors influencing puffing intensity - these will include differences in cigarette draw resistance, taste, and acceptability of the test brand to the smoker. Nonetheless, this is an area in which further carefully controlled experimentation would be profitable, particularly with cigarettes of similar strengths but differing ratios of ingredients.

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TABLE 2

Values of X^2 for the association between direction of change in cigarette yield, smoke nicotine concentration and measures of puffing intensity.

	Puff Volume	Puff Frequency	Total volume Puffed
Nicotine Yield of Cigarette	0.23	0.03	1.45
Smoke Nicotine Concentration	1.42	0.06	1.50

Values of X^2 have been corrected for continuity. For significance at $P < 0.05$ a value of X^2 of 3.84 is required.

Plasma nicotine and puffing intensity

In contrast to changes in cigarette smoke composition, variation in plasma nicotine levels appears to have no effect on the intensity with which individual cigarettes are smoked. Periods of a few hours smoking deprivation, sufficient to produce a significant fall in plasma nicotine levels, have no effect on the puff volume and frequency of puffing from subsequent cigarettes (39). This finding is corroborated by the results of an experiment in which nicotine was administered intravenously while subjects puffed from a continually-replaced cigarette (16). No changes in puff volume or puff frequency were detected during or after the pulsed injection of nicotine boli, whereas inhaled doses of smoke from a cigarette of a different composition to that of the continually-replaced brand produced large, transient excursions from the mean level of puff volume and puff frequency. We infer that among these subjects the primary effect of the intensity of puffing was to influence cigarette smoke composition rather than to titrate nicotine uptake, and we cite these results as further support for our hypothesis.

CONCLUSIONS

Nicotine is the only proven psychopharmacologically-active ingredient in cigarette smoke (1) and we have no reservations that it is a controlling factor in overall cigarette consumption, as measured by the number of cigarettes smoked per day. We have, however, demonstrated that the published data on human smoking behaviour is consistent with nicotine playing an additional role, which we suggest is attributable to a local action of nicotine on irritant receptors in the airways. The evidence for this hypothesis is found in a wide range of studies,

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and the hypothesis explains results which are hard to interpret under the nicotine self-titration model: we have shown why cigarettes with a higher content of nicotine are paradoxically smoked more intensively, and have explained the 'anomalous' finding that nicotine administered intravenously has no effect on puffing intensity.

Our hypothesis has implications both for the design of 'safer' cigarettes, and for the advice given to smokers to enable them to minimise their health risks if they persist in smoking. Smokers who are unable to give up the habit have been recommended to smoke low-tar cigarettes with enhanced nicotine yields (40,41). If, as we believe, the smoke from such cigarettes is easier to inhale, the smoker may as a result increase his exposure to other toxic ingredients in tobacco smoke. Supporting evidence for this assertion comes from a brand-switching study, in which an increased retention of carbon monoxide was observed when subjects switched to an enhanced-nicotine cigarette (11).

Among cigarettes manufactured in the United Kingdom the average sales-weighted nicotine content of the smoke, expressed as a percentage of tar, has been increasing steadily since 1974 (42), largely as a result of the popularity of low-tar cigarettes with a medium delivery of nicotine. Among currently-available American cigarettes, brands with lower machine-smoked nicotine yields actually contain tobacco with a higher nicotine concentration than is found in the higher-yielding brands (38), and almost certainly deliver smoke in which the particulates have a high nicotine content. The fact that these modifications to cigarette design have been accompanied by a decline in machine-smoked tar yields has elicited the approval of statutory Government health agencies. We recommend that before encouraging further changes in the composition of cigarette smoke, we should improve our understanding of the factors that determine all aspects of smoking behaviour.

Acknowledgement

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